REMARKS

Any fees that may be due in connection with this application may be charged to Deposit Account No. 06-1050. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 1-6, 9-34, 40-51, 54-61 and 63-72, 78, 82-94 and 102-107 are pending in this application. Claims 102-107 are amended herein to correct minor typographical errors. No new matter is added by this amendment.

INFORMATION DISCLOSURE STATEMENT

The Office Action indicates that the IDS mailed February 19, 2004 contains a list of U.S. patents with "wrong US patent numbers" and "irrelevant documents" that are not prior art. The Office Action asserts that "the statements filed clearly do not comply with the guidelines set forth in MPEP 2004." The Office Action cites case law stating, "the cloaking of a clearly relevant reference by inclusion in a long list of citations may not comply with Applicant's duty of disclosure."

Regarding the suggestion that Applicant is "cloaking" a reference, Applicant has submitted references in good faith in compliance with 37 C.F.R. §1.56 and MPEP §2004. References may be material, if, for example, they are cited in corresponding or related applications; if they are publications by an inventor of the applications; if they could raise issues of obviousness-type double patenting; if they could raise issues under 35 U.S.C. §102(f) or (g). The decision regarding the actual relevance of a document is a legal determination to be made by the Office and subsequently by the courts. The undersigned has detailed procedures in place to ensure that all such information is provided to the Patent Office.

Regarding the "wrong US patent numbers," the IDS mailed February 19, 2004, provides a list of 28 U.S. patent publications from Ref. Code A through Ref. Code AB. The document numbers indicated on the Form PTO-1449 are the U.S. patent publication numbers with the numerals representing the publication year (i.e., the first four numerals) removed. In the event that this listing of U.S. patent publications in Form PTO-1449 might be unclear, attached herewith is a reformatted Form PTO-1449 citing the same references as the Form

PTO-1449 mailed February 19, 2004, and clearly indicating the publication number of these previously submitted 28 U.S. patent publications.

Regarding the allegedly "irrelevant documents," 37 C.F.R. §1.56 establishes a duty to disclose information material to patentability, not only information that may be art that is published prior in time. Nearly all documents cited in the IDS are owned by Sequenom, Inc., the assignee of the present application, and/or name at least one inventor that also is named in the present application. As stated in MPEP §2004:

> "Do not rely on the examiner of a particular application to be aware of other applications belonging to the same applicant or assignee. It is desirable to call such applications to the attention of the examiner even if there is only a question that they might be 'material to patentability' of the application the examiner is considering."

Hence, the documents identified in the IDS mailed February 19, 2004 were submitted in good faith for consideration by the Examiner in compliance with 37 C.F.R. §1.56 and MPEP §2004. Any assertion of "cloaking" a reference is therefore inconsistent with USPTO policies.

THE REJECTION OF CLAIMS 43 AND 44 UNDER 35 U.S.C. §112, FIRST PARAGRAPH FOR LACK OF ENABLEMENT

Claims 43 and 44 are rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable one skilled in the art to practice a claim that does not recite the presence of analyte, matrix and solvent in a single fluid deposited on the surface of a substrate. This rejection is respectfully traversed.

RELEVANT LAW

In order to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

ANALYSIS

The specification enables the full scope of claims 43 and 44 as written. The specification teaches that analyte and matrix can be dispensed in the same solution or in different solutions. For example, the specification, at page 6, last paragraph, teaches first dispensing fluid containing matrix onto a substrate, and then adding fluid containing analyte to the substrate. In another example, the specification, at the paragraph spanning pages 20-21, teaches methods in which analyte solution is first dispensed onto a substrate, followed by dispensing matrix solution. The specification also teaches methods of dispensing solutions that contain both matrix and analyte. Claims 43 and 44 encompass all such embodiments.

The Office Action states, "Claims 43 and 44 recite that the fluid comprises only solvent and the matrix material, without mentioning the sample material." Applicant disagrees, and submits that claims 43 and 44 do not require that the fluid comprise only solvent and matrix. Claim 43 recites, "A method of claim 40, wherein the fluid comprises a solvent and a matrix material." Claim 40 does not require that the fluid contain only solvent and the matrix, nor does claim 44. The term "comprises" is inclusive language and does not exclude additional, unrecited elements (MPEP §2111.03). Thus, claims 43 and 44 encompass dispensing a fluid containing analyte and matrix, and also encompass dispensing analyte onto a substrate before or after matrix is dispensed onto the substrate. All such embodiments are disclosed in the specification. The Office Action does not dispute Applicant's previous assertion that all such embodiments are disclosed and fully enabled by the specification.

The entire teachings of the specification must be considered to determine whether an unclaimed feature must be recited for the claim to be enabled (*In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976)). Enablement rejections based on the grounds that a disclosed critical limitation is missing from a claim "should be made only when the language of the specification makes it clear that the limitation is critical for the invention to function as intended." (MPEP §2164.08(c)). Broad language in the specification tends to rebut the argument of criticality.

The specification teaches that dispensed fluid can contain matrix, analyte, or both, and that matrix can be dispensed onto a substrate prior to dispensing an analyte, subsequent to dispensing an analyte, or simultaneously with an analyte. Thus, rejecting claims 43 or 44 for

not reciting dispensing analyte and matrix in the same fluid is inconsistent with the teachings of the specification. Accordingly, the rejection of claims 43 and 44 is inconsistent with court and USPTO interpretations of 35 U.S.C. §112, first paragraph.

THE REJECTION OF CLAIMS 1-4, 6, 9, 10, 14, 15, 25-28 and 30 UNDER 35 U.S.C. §102(b)

Claims 1-4, 6, 9, 10, 14, 15, 25-28, and 30 are rejected under 35 U.S.C. §102(b) as being anticipated by Zhang *et al.*, J. Mass Spec. 30:1768-1771 (1995) because Zhang *et al.* allegedly discloses dispensing material on a multi-well sample holder by moving a vesicle from spot to spot without touching the sample holder, and ejecting a defined and controlled volume of fluid such that MALDI spectra obtained from the spots are reproducible. This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure of each element of the claim under consideration in a single prior art reference. In re Spada, 15 USPQ2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 209 USPQ 288, 293 (CCPA 1981). Moreover, it is incumbent on the Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984).

ANALYSIS

The Claims

Claim 1

Independent claim 1 is directed to:

> A method for forming an array of a sample material on a surface of a substrate and analyzing the sample material in the resulting array, comprising:
> providing a vesicle that has an interior chamber containing a fluid comprising a solvent containing the sample material;
> disposing said vesicle adjacent to a first location on said surface of the substrate without contacting the surface with the vesicle;
> providing mechanical pressure to the interior of the vesicle to eject from said chamber a defined and controlled 0.2 to 20 nanoliter volume of the fluid to dispense said fluid at said first location of said surface of the substrate;
> moving said vesicle to each of a set of positions adjacent to the surface of the substrate, whereby a defined and controlled 0.2 to 20 nanoliter volume of fluid is

dispensed at each location of said set forming an array of spots of sample material on the substrate such that spot-to-spot characteristics are reproducible in the array; and

performing mass spectrometry analysis of the sample material at each location of the array, wherein mass spectra of the sample obtained from each spot are reproducible within the array of spots.

Claim 25

Independent claim 25 is directed to:

A method for analyzing a material, comprising:

providing a vesicle comprising a fluid containing the material in a solvent;

disposing said vesicle adjacent to a first location of a surface of a substrate without contacting the surface with the vesicle;

delivering a defined and controlled nanoliter volume of the fluid at the first location of said surface of the substrate;

moving said vesicle to a second position next to the first location on said surface of the substrate to dispense a defined and controlled nanoliter volume of said material along an array of locations on said substrate surface to form an array of the material such that spot-to-spot characteristics are reproducible in the array; and

performing mass spectrometry analysis for said material at each location of said array, wherein mass spectra of the material obtained from each spot are reproducible within the array of spots.

All other claims rejected under U.S.C. 102(b) depend from claims 1 and 25, and thus contain all elements of the respective independent claim.

Disclosure of the cited reference

Zhang *et al.* discloses a concentrating and desalting procedure for improving mass spectra. Zhang *et al.* discloses that in order to achieve high sensitivity for some biological samples, a dilute sample should be concentrated to a small volume (e.g., 5-10 nl), and salts should be removed during the volume reduction procedure (page 1768, left column, lines 10-16). Zhang *et al.* discloses a C_{18}-packed fused-silica capillary as a multi-functional device for micro-concentration, desalting and matrix addition (page 1768, right column, lines 1-4). Zhang *et al.* discloses that salts can be washed from the capillary and peptides eluted with an organic solvent that contains MALDI matrix to achieve sample spot sizes of about 5 nl (page 1768, right column, lines 4-7). Zhang *et al.* concludes that sample preparation for MALDI analysis is a critical step in achieving high sensitivity and reproducibility (page 1771, left column, lines 11-13), and states, "In particular, a micro-preconcentration/desalting/fractionation procedure can be used effectively for the analysis of trace levels of peptides containing

physiological levels of salts." (page 1771, left column, lines 13-16). Sample is loaded on the the column, desalted, and is eluted in concentrated form in small volumes. The actual volume itself is not critical.

Zhang *et al.* discloses nothing about disposing a vesicle adjacent to a substrate without contacting the surface of the substrate. Zhang *et al.* discloses nothing about a dispensing a defined and controlled volume. Zhang *et al.* discloses nothing about reproducible spot-to-spot characteristics.

Disclosures incorrectly attributed to the cited reference

On several occasions, the Office Action asserts particular disclosures by Zhang *et al.*, but the reference contains no such disclosures. None of the following assertions regarding Zhang *et al.* are present in the reference.

The Office Action states, "This is in a complete contradiction to Zhang 's disclosure, cited twice by the examiner in two Office actions: 'into each well [which assumes an array of wells] was dispensed 20 droplets (~5 nL) of 3-HPA matrix solution' (page 26, the last paragraph)." Zhang *et al.* has no such disclosure. Zhang *et al.* has no page 26. The quoted text is not from Zhang *et al.*, but is instead from Applicant's specification. Similarly, in another location, the Office Action states, "That Zheng's [*sic*] disclosure does not indicate that the same volume of ~5 nL is deposited in each well, as mentioned by the Applicant, is simply not true." The examiner recited this quote many times: 'into each well was dispensed 20 droplets (~5 nL) of 3-HPA matrix solution'." This quote is found only in Applicant's specification.

In another instance, the Office Action rhetorically asks, "How does not Zheng [*sic*] describe or address arrays, when the drawing clearly shows these arrays and Zheng [*sic*] is referring to 'each well' of the multi-well substrate?" Nowhere does Zhang *et al.* contain the phrase "each well." Such a phrase is only present in arguments made in a previous Office Action.

In yet another instance, the Office Action states, "As for contacting the vesicle with the substrate: formation of a droplet (disclosed by Zheng [*sic*]) requires non-contacting interaction between the vesicle and the substrate." Zhang *et al.* never discloses formation of a droplet. The Office Action makes no attempt to identify the alleged disclosure.

None of these alleged disclosures of Zhang *et al.* are present in the reference. Accordingly, rejections that rely on these incorrectly attributed disclosures must fail for lack of support.

Claim elements absent from cited reference

Zhang *et al.* cannot anticipate the claimed methods because Zhang *et al.* does not disclose all elements of the claims. Zhang *et al.* fails to disclose disposing a vesicle adjacent a substrate without contacting the surface of the substrate. Zhang *et al.* fails to disclose dispensing a defined and controlled volume. Zhang *et al.* fails to disclose reproducible spot-to-spot characteristics. Each claim element is discussed in turn.

"Without contacting"

Claims 1 and 25 recite disposing a vesicle adjacent a substrate without contacting the surface of the substrate. Zhang *et al.* is silent as to contacting or not contacting the substrate. In asserting that Zhang *et al.* anticipates this element, the Office Action states, "No contacting of the vesicle with the substrate for disposing the liquid is indicated in the reference." For further support, Office Action asserts, "As for contacting the vesicle with the substrate: formation of a droplet (disclosed by Zheng [*sic*]) requires non-contacting interaction between the vesicle and the substrate." Zhang *et al.* never discloses formation of a droplet. Accordingly, the Office Action, in finding this element anticipated by Zhang *et al.*, points to (1) a lack of disclosure by the reference and (2) an alleged disclosure not present in the reference. Anticipation requires the disclosure of each element of the claim under consideration in a single prior art reference. The Office Action has not pointed to any disclosure in the cited reference of disposing a vesicle adjacent a substrate without contacting the surface of the substrate. Zhang *et al.* does not disclose disposing a vesicle adjacent a substrate without contacting the surface of the substrate. Thus, Zhang *et al.* cannot anticipate the claims.

In further support of the anticipation rejection, the Office Action asserts that the element of not contacting the substrate would have been obvious to one skilled in the art. The Office Action states, "Moreover, contacting vesicle with the substrate would lead to the vesicle contamination, the fact obvious for anyone of ordinary skill in the art." The reference does not disclose not contacting a substrate, nor any consideration of contamination by

contacting a substrate. The Office Action does not assert that "not contacting" is inherent in Zhang *et al.* Instead, the Office Action takes the position that this claim element is anticipated because it would have been obvious to one of ordinary skill in the art. If a claim element is neither disclosed nor inherent in a reference, the reference does not anticipate the claim; what would have been obvious is insufficient. Accordingly, an anticipation rejection based on what would have been obvious in view of Zhang *et al.* cannot be sustained.

"Defined and controlled volume"

Claims 1 and 25 recite dispensing a defined and controlled volume. Zhang *et al.* does not disclose dispensing a defined and controlled volume. Zhang *et al.* merely discloses desalting and concentrating samples to a "small volume (e.g., 5-10 nl)" (page 1768, left column, lines 10-16), and sample spot sizes of "about 5 nl." (page 1768, right column, lines 4-7).

The Office Action impermissibly imports limitations into the claims from Applicant's specification. The Office Action states, "Zheng [*sic*] discloses highly precise and reproducible arrays of droplets of ~5 nL, the volume disclosed in the instant specification." The Office Action points to Zhang *et al.*'s disclosure of spot sizes of "about 5 nl" (page 1768, right column, lines 4-7) and Figure 1 of Zhang *et al.*, which shows a MALDI-MS sample holder. The Office Action does not point to any disclosure in Zhang *et al.* of "highly precise and reproducible arrays" or of dispensing a defined and controlled volume, as recited in claims 1 and 25.

Instead, the Office Action imports into the claims a specific embodiment in Applicant's specification as a substitute for the language of the claims. The Office Action states, "Zhang is dealing with an array of precisely deposited small volume droplets (~5 nL, exactly the same precision of the volume of droplets disclosed in the instant application), indicating reproducibility and high sensitivity of such arrays for MALDI analysis." The Office Action cites to one experimental example in the instant specification, which teaches dispensing "20 droplets (~5 nL)" into each well of a silicon chip (page 26, last paragraph). The Office Action appears to indicate that the meaning of "defined and controlled" is controlled by the Office Action's interpretation of "~5 nL" in the specification. Accordingly, the Office Action fails to consider the claims as written, and instead imports a limitation from

the specification into the claims, which is not allowed. Without importing this limitation into the claims, Zhang *et al.* cannot anticipate the claims because Zhang *et al.* does not disclose dispensing a defined and controlled volume.

The method disclosed in the instant application for dispensing a defined and controlled volume is different than the disclosure of Zhang *et al.* The specification is directed to methods for dispensing controlled and defined volumes, and provides several apparatuses and methods for dispensing defined and controlled volumes. The specification discloses robot-driven serial and parallel pL-nL dispensing tools that were used to generate arrays on chips for matrix assisted laser desorption ionization mass spectrometry analysis (page 23, first full paragraph). For example, the specification, at the paragraph spanning pages 11-12 and at Figure 2, discloses a pin assembly in which fluid can be drawn into and ejected from the interior chambers of the pins. The specification discloses that a data processor can run a computer program that directs a controller to eject a defined volume of fluid from the pins (page 17, top paragraph). The specification also discloses that the volume of fluid held by each pin can be controlled by selecting the dimensions of the interior bore of the pin (page 16, top paragraph). The specification also discloses jet assemblies for dispensing defined and controlled the volumes that use piezoelectric transducers, electric transducers, electrorestrictive transducers, magnetorestrictive transducers, or electromechanical transducers (page 18, first full paragraph, and Figure 6). The specification discloses an exemplary piezoelectric pipette that dispenses single or multiple 0.2 nL droplets onto a chip (page 23, first full paragraph). Thus, the specification provides specific devices, methods and guidance for delivering defined and controlled volumes to the surface of a substrate. Zhang *et al.* does not disclose any apparatus, method or guidance for dispensing defined and controlled volumes. Zhang *et al.* merely discloses elution with syringes and syringe pumps at a flow rate of 0.1 μl/min. No mention is made of a device that delivers the defined volume (e.g., pin or piezoelectric pipette). No mention is made of a device that controls the amount of volume delivered (e.g., a data processor that can run a computer program that directs a controller to eject a defined volume). There is no mention by Zhang *et al.* that a defined and controlled volume is important, since Zhang *et al.* merely teaches the importance of concentrated, low-volume samples. Accordingly, the disclosure by Zhang *et al.* of a spot size

of "about 5 nl" is not a disclosure of dispensing a defined and controlled volume as described in Applicant's specification and recited in the claims.

"Reproducible spot-to-spot characteristics"

Claims 1 and 25 recite dispensing a defined and controlled volume along an array such that spot-to-spot characteristics are reproducible. Zhang *et al.* does not disclose dispensing a defined and controlled volume along an array such that spot-to-spot characteristics are reproducible. Zhang *et al.* discloses desalting and concentrating samples to a "small volume (e.g., 5-10 nl)" (page 1768, left column, lines 10-16), and sample preparation is critical for reproducibility. (page 1771, left column, lines 11-13).

The Office Action incorrectly characterizes the reference as disclosing spot-to-spot reproducibility. The Office Action asserts, "Moreover, Zheng absolutely unambiguously indicates that the volume of the sample is essential for reproducibility of the results, again in opposition to what the Applicant claims." The Office Action points to the disclosure of Zhang *et al.* that sample preparation is a critical step in achieving reproducibility, and the Office Action asserts that sample preparation by Zhang *et al.* means removal of salts and decreasing the volume of the sample. Zhang *et al.* discloses that desalting and concentrating the sample by reducing the volume increased MALDI sensitivity (page 1769, paragraph spanning left and right columns). Zheng *et al.* demonstrates that ***sample concentration, not volume***, is important; this is shown in Zhang *et al.*'s disclosure that a "normal loading volume, i.e. about 0.5 μl" having a sufficient amount of analyte could generate a "similar signal to noise recording" relative to a lower volume sample with less analyte (page 1770, sentence spanning left and right columns). Thus, the "reproducibility" disclosed in Zhang *et al.* does not result from the volume of each spot, but instead from the removal of salts and the concentration of analyte in the sample, regardless of volume.

Zhang *et al.* is silent as to reproducible volumes between spots. Zhang *et al.* is silent as to dispensing a defined and controlled volume for any spot. Accordingly, the Zhang *et al.* does not disclose dispensing a defined and controlled volume along an array such that spot-to-spot characteristics are reproducible.

In further support of the anticipation rejection, the Office Action asserts that the element of reproducible spot-to-spot characteristics would have been obvious to one skilled

in the art. The Office Action asserts, "The main idea of the instant disclosure is that the volumes of the deposited droplets should be in nL range in order to get reproducible results, not that they should be the same; the latter is obvious for any ordinary person, even the one not skilled in the art." The reference does not disclose dispensing a defined and controlled volume of fluid such that spot-to-spot characteristics are reproducible. The Office Action does not assert that this element is inherent in Zhang *et al.* Instead, the Office Action asserts that such a step is obvious to one of ordinary skill in the art. If a claim element is neither disclosed nor inherent in a reference, the reference does not anticipate the claim; what would have been obvious is insufficient. Accordingly, an anticipation rejection based on what would have been obvious in view of Zhang *et al.* cannot be sustained.

THE REJECTIONS UNDER 35 U.S.C. §103(a)

The Rejection of Claims 11-13, 29, 31-34, 40-42, 47, 51, 54-59, 61, 63-72, 82-85 and 87-94 as Obvious over Zhang *et al.* and Nelson *et al.*

Claims 11-13, 29, 31-34, 40-42, 47, 51, 54-59, 61, 63-72, 82-85 and 87-94 are rejected as unpatentable over Zhang *et al.* and Nelson *et al.* (U.S. Pat. No. 5,955,729) because the teachings of Nelson *et al.* regarding guide pins, an ink-jet applicator, and an automated delivery flow system allegedly combine with the teachings of Zhang *et al.* to render the claims obvious. The rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed subject matter. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. E*x parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp.*

Systems, Inc. v. Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 929, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

Also, it is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole. *In re Sernaker*, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). Unexpected properties must always be considered when determining obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesh*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

ANALYSIS

Claims

Claims 11-13

Claim 11 is directed to the method of claim 1, discussed above, wherein the vesicle is part of a vesicle assembly having a plurality of vesicles arranged into a matrix for dispensing fluid to a first plurality of locations onto said substrate surface. Claims 12 and 13 depend from claim 11.

Claim 29

Claim 29 is directed to the method of claim 25, discussed above, wherein said step of performing mass spectrometry includes the step of performing a time of flight mass spectrometry analysis.

Claims 31-34 and 92

Claim 31 is directed to a system for forming an array of a sample material on a surface of a substrate and analyzing the sample material in the array, comprising:

a vesicle having a distal end suitable for carrying a nanoliter of fluid;

a movable arm having a distal portion mounted to move said vesicle;

a controller for moving said arm to dispose said vesicle adjacent to a first location on said surface of the substrate and for controlling said vesicle to deliver a defined and controlled 0.2 to 20 nanoliter volume of the fluid at said first location of said surface of the substrate; and

a mass spectrometer for analyzing said material deposited on said surface of said substrate, wherein mass spectra of the sample material obtained from each spot are reproducible within the array of spots.

Claims 32-34 and 92 depend from claim 31.

Claims 40-42, 47, 51, 54-59, 61, 63-69 and 93

Claim 40 is directed to a method for dispensing sub to low nanoliter volumes of a material as an array onto the surface of a substrate, comprising the steps of:

(a) providing an assembly having a plurality of vesicles arranged in the form of an array for dispensing a liquid therefrom, wherein each vesicle has an interior chamber containing a fluid containing the material;

(b) aligning the vesicles at a first set of locations adjacent to the surface of the substrate without contacting the surface with the vesicles;

(c) using mechanical pressure, controlling each of the chambers to eject a defined and controlled 0.2 to 20 nanoliter volume of the fluid from each vesicle onto the surface of the substrate aligned with the vesicles, whereby an array of spots of the fluid is deposited on the surface of the substrate, such that spot-to-spot characteristics are reproducible in the array; and

(d) providing the resulting substrate with the array of material deposited thereon to a mass spectrometer and determining information representative of the composition of the deposited material, wherein mass spectra of the material obtained from each spot containing analyte are reproducible within the array of spots.

Claims 41, 42, 47, 51, 54-59, 61, 63-69 and 93 depend from claim 40.

Claims 70-72 and 94

Claim 70 is directed to a method for dispensing nanoliter volumes of a material as an array on the surface of a substrate and analyzing the material in the array, comprising the steps of:

(a) providing a pin assembly having a plurality of elongated vesicles arranged as an array for dispensing a liquid therefrom, wherein each vesicle comprises a solid shaft of material having an end for retaining a nanoliter volume of fluid;

(b) loading a nanoliter volume of fluid comprising a liquid material from a fluid source onto the end of the vesicles of the pin assembly;

(c) disposing the pin assembly to align the vesicles at a first set of locations adjacent to a surface of the substrate without contacting the surface with the vesicles;

(d) contacting the loaded fluid to the surface of the substrate aligned with the vesicles to deposit a defined and controlled 0.2 to 20 nanoliter volume at each location, whereby an array of spots of material on the surface of the substrate is formed, such that spot-to-spot characteristics are reproducible in the array; and

(e) analyzing the array of material on the surface of the substrate by mass spectrometry, wherein:

mass spectra of the material obtained from each spot are reproducible within the array of spots;

the substrate comprises matrix material;

the fluid comprises analyte material;

the fluid of analyte material at the end of the vesicles is contacted with the evaporated matrix material on the surface of the substrate to dissolve the matrix material with the analyte material and thereby deposit a mixture of matrix and analyte material.

Claims 71, 72 and 94 depend from claim 70.

Claims 87-91

Claims 78-91 are directed to the method of claim 1, where claim 87 further provides that the vesicle is part of an assembly of vesicle elements, wherein each vesicle comprises an

interior chamber holding the 0.2 to 20 nanoliter volumes of fluid, and claim 88 depends from claim 87.

Claim 89 further provides that the vesicle has an interior chamber and forms part of an assembly comprising a plurality of vesicles and a transducer element mounted to each vesicle for driving fluid through the interior chamber to eject fluid by deforming the chamber; and

the transducer element deforms the chamber with sufficient pressure to spray the fluid from the pin or to cause a drop of fluid to extend from the chamber so that fluid can be passed to the substrate by contacting the drop to the surface of the substrate.

Claim 90 further provides that the method of claim 1 is automated.

Claim 91 further provides that the mass spectrometry format is matrix assisted laser desorption ionization mass spectrometry.

Teachings of the cited references

Zhang *et al.*

The reference by Zhang *et al.* is described above.

Nelson *et al.*

Nelson *et al.* teaches methods for carrying out surface plasmon resonance mass spectrometry. The method taught by the reference includes use of a molecular interaction analysis (IA) surface containing antibodies, passing sample through a flow channel containing the antibodies, and detecting binding of the antibodies by a change in the intensity of the reflected light versus angle of incidence. One such IA surface of the reference is an IA sensor chip with a plurality of interactive surfaces in contact with individual flow cells, where samples and reagents are delivered to the chip surface by an automated flow system.

The reference teaches that the IA sensor chip can be used as the sample stage for mass spectrometry. The reference provides that matrix can be added to the chip using a matrix applicator containing multiple surfaces to which matrix is applied, and then the matrix applicator surfaces are placed in contact with the sensor chip. Matrix can also be applied using an ink jet applicator where the "ink" contains matrix.

The rejected claims are not *prima facie* obvious in view of the cited art

It is respectfully submitted that the teachings of the references singly or in any combination thereof do not result in claimed methods or systems. Therefore, the Office Action has failed to set forth a *prima facie* case of obviousness.

Claims 11-13, 29, 40-42, 47, 51, 54-59, 61, 63-72, 82-85, 87-89, 91, 93 and 94

Claims 11-13, 29, 40-42, 47, 51, 54-59, 61, 63-72, 82-85, 87-89, 91 93 and 94 are directed to methods of forming an a array of material on the surface of a substrate, using either a plurality of vesicles arranged in a matrix or an array, or using an assembly of vesicles. In each of the claimed methods, the plurality or assembly of vesicles are disposed adjacent to the surface of the substrate without contacting the surface of the substrate. Each of the claimed methods also recites ejecting or delivering a defined and controlled volume such that spot-to-spot characteristics are reproducible in an array. The combination of teachings of the references fails to teach or suggest plurality or assembly of vesicles are disposed adjacent to the surface of the substrate without contacting the surface of the substrate. The references also fail to teach or suggest ejecting or delivering a defined and controlled volume such that spot-to-spot characteristics are reproducible in an array.

Disposing or Aligning a Plurality or Assembly of Vesicles Adjacent to the Surface of the Substrate Without Contacting the Surface of the Substrate

Neither Zhang *et al.*, Nelson *et al.*, nor any combination thereof, teaches or suggests disposing or aligning a plurality or assembly of vesicles adjacent to the surface of the substrate without contacting the surface. The Office Action does not assert that Zhang *et al.*, Nelson *et al.*, or a combination thereof, teaches or suggests disposing or aligning a plurality or assembly of vesicles adjacent to the surface of the substrate without contacting the surface. Instead, the Office Action asserts that a plurality of vesicles would have been an obvious modification of the references "because this is an obvious advantage regarding the speed and efficiency of the method of forming MALDI-MS substrate." This statement represents an entry of evidence into the record by judicial notice. In an obviousness rejection, deficiencies of the cited references cannot be remedied by general conclusions by the Office Action about what is "basic knowledge" or "common sense" to one of ordinary skill in the art. *In re Zurko*,

59 USPQ2d 1693, 1697 (Fed. Cir. 2001). Rather, the Office Action must point to some concrete evidence in the record in support of these findings. *Zurko*, at 1697. In Applicant's previous response, Applicant traversed the previous Office Action's assertion by judicial notice; however the present Office Action fails to provide supporting documentary evidence. Instead, the Office Action demonstrates a lack of understanding of the *Zurko* requirements in taking judicial notice by stating:

> It is not quite clear for the examiner how the Applicant 's general statement, 'improvements in MALDI-MS substrate production are neither basic knowledge nor arise simply from common sense, and methods of MALDI-MS substrate production fall outside of the expertise of the PTO to determine in the absence of supporting evidence', should be interpreted by the examiner. Does it mean that any routineer in the art possesses only 'basic knowledge' and 'common sense'? This is not a correct definition of a person 'skilled in the art'.

This response to Applicant's traversal fails to provide any documentary evidence supporting the proposed modification of the references, and, thus, fails to carry the required burden for establishing an obviousness rejection. Therefore, in accordance with MPEP §2144.03 ("If applicant adequately traverses the examiner's assertion of official notice, the examiner must provide documentary evidence in the next Office action if the rejection is to be maintained.") and *Zurko*, 258 F.3d at 1386, 59 USPQ2d at 1697 ("[T]he Board [or examiner] must point to some concrete evidence in the record in support of these findings" to satisfy the substantial evidence test.), this rejection cannot be maintained.

Defined and controlled volume such that spot-to-spot characteristics are reproducible

Neither Zhang *et al.* or Nelson *et al.*, singly or in any combination thereof, teaches or suggests dispensing a defined and controlled volume onto the surface of a substrate such that spot-to-spot characteristics are reproducible in an array. As discussed above, Zhang *et al.* does not teach or suggest dispensing a defined and controlled volume onto the surface of a substrate such that spot-to-spot characteristics are reproducible in an array.

Nelson *et al.* does not provide that which is lacking in Zhang *et al.* Nelson *et al.* teaches a sample flow cell on a substrate and dispensing matrix on the surface of the substrate. Nelson *et al.* provides no teaching or suggestion of dispensing a defined and controlled volume onto the surface of a substrate such that spot-to-spot characteristics are

reproducible in the array. Because Nelson *et al.* is silent on this claim element, combining Nelson *et al.* with Zhang *et al.* provides no additional teaching or suggestion of this claim element when the references are combined. Therefore, because the teachings of the cited references, alone or combined, do not result in the claimed subject matter, the Office Action cannot set forth a *prima facie* case of obviousness.

Notwithstanding this failure, there would have been no motivation to have combined the teachings of the cited references nor to do what applicant has done

Even if all elements of the claimed methods were taught or suggested by the combination of references, one of ordinary skill in the art would not have been motivated to have combined the teachings cited references in such a way to arrive at the claimed methods or systems. The Office Action asserts that it would have been obvious to use the ink-jet applicator of Nelson *et al.* in the method of Zhang *et al.* However, such a combination would go against the teachings of Nelson *et al.*

Zhang *et al.* teaches mass spectrometry sample preparation by elution methods (page 1769, left column, lines 2-8). Zhang *et al.* teaches only elution using syringe pumps (page 1768, right column, lines 13-14), and suggests nothing about desirable devices or methods for dispensing eluate onto a target. Nelson *et al.* teaches the importance of not eluting sample from the sample capture surface in preparing the sample for mass spectrometry (column 9, lines 29-31), and that an ink-jet applicator can be used for adding matrix to the sample capture surface (column 10, lines 18-22). Thus, Nelson *et al.* teaches that sample should not be eluted.

The Office Action asserts that it would have been obvious to elute samples using the ink-jet applicator of Nelson *et al.* Zhang *et al.* provides no motivation for any particular method of eluting sample. Moreover, this modification goes against the teachings of Nelson *et al.* since Nelson *et al.* teaches that sample should not be eluted. Without the teachings of the cited art suggesting the combination, it is impermissible to pick and choose among isolated disclosures in the prior art to conclude that the claimed subject matter is obvious. No motivation exists to combine the references as suggested in the Office Action; if anything, the cited references teach against the combination. Accordingly, the isolated disclosures of the

references cannot be combined in the manner suggested by the Office Action to render the claimed methods *prima facie* obvious.

Claims 31-34 and 92

Claims 31-34 and 92 recite systems containing a vesicle having a distal end, a movable arm having a distal portion mounted to move the vesicle, a controller for moving the arm and for controlling the vesicle to deliver a defined and controlled volume to the surface of a substrate, and a mass spectrometer for analyzing material deposited on the surface of the substrate, where mass spectra from each spot are reproducible within the array of spots.

The Office Action provides no basis for rejecting these claims as *prima facie* obvious. The Office Action does not point to Zhang *et al.* or Nelson *et al.* for a teaching or suggestion of a movable arm, a controller for moving a movable arm, or a controller for controlling a vesicle to deliver a defined and controlled volume to the surface of a substrate. This deficiency was noted in Applicant's previous response. The present Office Action, in answering Applicant's response, only states, "In the rest of the arguments the Applicant seems to attack each reference individually, which does not comply with the US patent practice: one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." This statement fails to advance prosecution and fails to establish claims 31-34 and 92 as *prima facie* obvious.

Regardless of the deficiencies of the Office Action, Zhang *et al.* and Nelson *et al.*, alone or combined, do not teach or suggest the systems of claims 31-34 and 92. Neither reference or combination thereof teaches or suggests any system that includes a vesicle having a distal end, a movable arm having a distal portion mounted to move the vesicle, a controller for moving the arm and for controlling the vesicle to deliver a defined and controlled volume to the surface of a substrate, and a mass spectrometer for analyzing material deposited on the surface of the substrate. Accordingly, notwithstanding the Office Action's failure to provide reasons for rejecting these claims, no combination of the cited references can be made to render claims 31-34 and 92 *prima facie* obvious.

Claim 90

Claim 90 is directed to the method of claim 1 that is automated. Claim 1 recites dispensing a defined and controlled volume onto the surface of a substrate such that spot-to-

spot characteristics are reproducible in the array. As discussed above, the teachings of Zhang *et al.* and Nelson *et al.*, alone nor combined, do not result in method including a step of dispensing a defined and controlled volume onto the surface of a substrate such that spot-to-spot characteristics are reproducible in the array.

Further, one of ordinary skill in the art would not have been motivated to have combined the teachings cited references in such a way to arrive at the claimed methods or systems. Nelson *et al.* teaches automating delivery of a sample to a flow cell of a chip that serves as the mass spectrometry target (column 8, lines 43-45). The method of Nelson *et al.* takes advantage of not eluting sample from the chip surface (column 9, lines 29-31). Zhang *et al.* teaches eluting a sample from a C_{18} capillary and spotting the eluate onto a mass spectrometry substrate (page 1769, left column, lines 2-8). If the method of Zhang *et al.* were replaced by the automated method of Nelson *et al.*, sample would no longer be eluted from the C_{18} capillary and spotted onto a mass spectrometry substrate. Thus, modifying the method of Zhang *et al.* by automating it in accordance with Nelson *et al.* would result in sample remaining in a C_{18} capillary and inaccessible to a mass spectrometer. The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. No such desirability is provided by any combination of the cited references. Therefore the Office Action has failed to set forth a *prima facie* case of obviousness of claim 90.

The Rejection of Claims 5, 45, 46, 48-50 and 78 as Obvious over Zhang I, Nelson *et al.* and Zhang II

Claims 5, 45, 46, 48-50 and 78 are rejected as allegedly obvious over Zhang *et al.*, J. Mass Spectrom. 30:1768-1771 (1995) (hereinafter Zhang I), Nelson *et al.*, U.S. Pat. No. 5,955,729, and Zhang *et al.*, J. Mass Spectrom. 31:1039-1046 (1996) (hereinafter Zhang II) because it allegedly would have been obvious to have used the matrix-precoated cellulose membrane of Zhang II with the combination of Zhang I and Nelson *et al.* described above.

Claims

Claim 5 is directed to a method for forming an array of a sample material on a surface of a substrate and analyzing the sample material in the resulting array, comprising:

providing a vesicle that has an interior chamber containing a fluid comprising a solvent containing material for deposition;

disposing said vesicle adjacent to a first location on said surface of the substrate without contacting the surface with the vesicle;

providing mechanical pressure to the interior of the vesicle to eject from said chamber a defined and controlled 0.2 to 20 nanoliter volume of the fluid to dispense solvent containing matrix material at said first location of said surface of the substrate, wherein the matrix material is for matrix-assisted laser desorption mass spectrometry;

moving said vesicle to each of a set of positions adjacent to the surface of the substrate, whereby a defined and controlled 0.2 to 20 nanoliter volume of solvent containing a matrix material is dispensed at each locus of the array;

waiting a predetermined period of time to allow the solvent containing the matrix material to evaporate on the surface of the substrate thereby depositing the matrix material on the surface;

moving said vesicle to each of a set of positions adjacent to the surface of the substrate, whereby a defined and controlled 0.2 to 20 nanoliter volume of fluid containing an analyte material is dispensed onto said evaporated matrix material at each locus of the array to dissolve with said matrix material and to form a crystalline structure at each locus of the substrate surface such that spot-to-spot characteristics are reproducible in the array;

performing mass spectrometry analysis of the sample material at each location of the array, wherein mass spectra of the material obtained from each spot are reproducible within the array of spots.

Claims 45-46 and 48-50 are directed to the method of claim 40, where claim 45 further recites waiting a predetermined period of time to allow solvent comprising the matrix material to evaporate from the fluid ejected onto the surface of the substrate leaving the matrix material deposited on the surface, and then repeating steps of (a) through (c) of claim 40 at the same locations on which the matrix material is deposited, wherein the chambers of the vesicles in the assembly contain a solvent comprising an analyte material, which upon ejection on the array of matrix material dissolves into the matrix.

Claim 46 recites that the method of claim 40 further includes

(d) moving the assembly of step (a) to align the vesicles at a second set of locations adjacent to the surface of the substrate;

(e) repeating step (c); and

(f) optionally repeating steps (d) and (e) to dispense fluid at additional sets of locations on the surface of the substrate, wherein steps of (a) through (f) are repeated at the same locations on which the matrix material is deposited, wherein the chambers of the vesicles in the assembly contain a solvent comprising an analyte material, which upon ejection on the array of matrix material dissolves into the matrix.

Claim 48 further recites that the fluid comprises an analyte in a solvent, and includes the further step of waiting a predetermined period of time to allow the solvent comprising analyte to evaporate from the fluid ejected onto the surface of the substrate leaving the analyte material deposited on the surface. Claim 49 is directed to the method of claim 49, further comprising repeating steps of (a) through (c) are repeated at the same locations at which analyte is deposited, wherein the chambers of the vesicles in the assembly contain a solvent comprising a matrix material, which upon ejection onto the array of analyte dissolves into the analyte.

Claim 50 recites that the method of claim 40 further includes

(d) moving the assembly of step (a) to align the vesicles at a second set of locations adjacent to the surface of the substrate;

(e) repeating step (c); and

(f) optionally repeating steps (d) and (e) to dispense fluid at additional sets of locations on the surface of the substrate, where the fluid comprises an analyte in a solvent;

the method includes the further step of waiting a predetermined period of time to allow the solvent comprising analyte to evaporate from the fluid ejected onto the surface of the substrate leaving the analyte material deposited on the surface; and

steps of (a) through (f) are repeated at the same locations at which analyte is deposited, wherein the chambers of the vesicles in the assembly contain a solvent comprising a matrix material, which upon ejection onto the array of analyte dissolves into the analyte.

References

Zhang I and Nelson *et al.*

Zhang I and Nelson *et al.* are described above.

Zhang II

Zhang II teaches continuous deposit of capillary electrophoresis effluent on a matrix-precoated cellulose membrane, with subsequent analysis using MALDI mass spectrometry. Zhang II teaches preparation of the matrix-precoated cellulose membrane by applying a solution containing matrix to a cellulose membrane fixed to the surface of a MALDI target plate to cover the membrane surface and then placing the membrane in a desiccator. Zhang II teaches mounting the membrane/target to a movable stage in contact with a capillary membrane strip. Zhang II teaches that the sample was loaded electrokinetically in conjunction with movement of the target plate.

Analysis

Claims 5, 45 and 46, are directed to methods in which a vesicle ejects matrix onto the surface of a substrate, and then steps are repeated with the vesicles ejecting analyte at the same locations on which matrix material is deposited. Claims 49, 50 and 78 are directed to methods in which a vesicle ejects analyte onto the surface of a substrate, and then steps are repeated with the vesicles ejecting matrix such that evaporated analyte material contacts the matrix material. Claim 48 is directed to a method of waiting a predetermined period of time to allow solvent to evaporate. All claims recite ejecting a defined and controlled volume onto the surface of a substrate such that spot-to-spot characteristics are reproducible in the array. The cited references do not render the methods of these claims obvious because the cited references, alone or combined, do not teach or suggest all elements of the claims.

Reproducible Spot-to-Spot Characteristics and Reproducible Mass Spectra

None of Zhang I, Nelson *et al.* and Zhang II, singly or in any combination thereof, teaches or suggests the methods of the rejected claims. As discussed above, Zhang I and Nelson *et al.*, singly or in combination, do not teach or suggest delivering a defined and controlled volume such that spot-to-spot characteristics are reproducible.

Zhang II does not cure these deficiencies. Zhang II teaches continuous deposition of sample onto a matrix-precoated membrane. Zhang II does not teach or suggest delivery of a defined and controlled volume. Zhang II does not teach or suggest an array of spots. Zhang II does not teach reproducible spot-to-spot characteristics. Accordingly, Zhang II does not

cure the deficiencies in the teachings of Zhang I and Nelson *et al.* Therefore, the cited references, alone or combined, do not teach or suggest the claimed methods.

Separately Ejecting Matrix and Analyte with the Same Vesicle

Claims 5, 45-46, 49-50 and 78 recite methods in which matrix and analyte are ejected onto a substrate surface in separate steps using the same vesicle. The cited references, alone or combined do not teach or suggest such a method. The Office Action does not even allege that any combination of the cited references teaches or suggests such a method.

Zhang I teaches eluting analyte onto a substrate surface using an eluent containing matrix. Thus, Zhang I teaches applying analyte and matrix to a substrate in the same step. Zhang I does not teach or suggest ejecting matrix and analyte onto a substrate surface in separate steps.

Nelson *et al.* teaches applying analyte to a substrate by flowing a sample over a substrate surface containing an antibody. Nelson *et al.* teaches applying matrix to the substrate by contacting the substrate with a matrix applicator or using an ink-jet applicator. Thus, Nelson *et al.* teaches using different instrumentalities to eject analyte and matrix onto the surface of a substrate. Nelson *et al.* does not teach or suggest ejecting matrix and analyte onto a substrate surface using the same vesicle.

Zhang II teaches pre-coating a membrane with MALDI matrix by covering the membrane with a matrix-containing solution. Zhang II teaches applying analyte to the membrane by electrokinetically loading sample from a capillary contacting the membrane strip. Thus, Zhang II teaches using different instrumentalities to eject analyte and matrix onto the surface of a substrate. Zhang II does not teach or suggest ejecting matrix and analyte onto a substrate surface using the same vesicle.

None of the references teaches or suggests ejecting matrix and analyte onto a substrate surface in separate steps using the same vesicle. No combination of the references teaches or suggests ejecting matrix and analyte onto a substrate surface in separate steps using the same vesicle. Thus, the cited references, alone or combined, do not result in the claimed methods. Accordingly, the cited references cannot establish a *prima facie* obviousness rejection of claims 5, 45, 46, 49, 50 or 78.

The Rejection of Claims 16-24 and 102-103 as Obvious over Zhang I and Hancock *et al.*

Claims 16-24 and 102-103 are rejected as obvious over Zhang I in view of Hancock *et al.*, U.S. Pat. No. 5,716,825. The Office Action asserts that the claims are obvious because Hancock *et al.* teaches the materials recited in claims 16-24, 102 and 103, while Zhang I teaches the underlying method. This rejection is respectfully traversed.

Claims

Claims 16-24 are directed to the method of claim 1, where the substrate contains silicon, a metal material, a plastic material, a membrane, a polymeric material, metal-grafted polymers, or a chemically functionalized substrate material, or is functionalized with beads or with a dendritic material. Claims 102 and 103 are directed to the methods of claims 1 and 25, respectively, where the substrate comprises any one of or combinations of silicon, metal, plastic, a membrane, polymeric material, a metal-grafted polymer; and the substrate is optionally functionalized chemically, functionalized with beads, functionalized with dendrite trees of captured material and combinations thereof.

References

Zhang I

Zhang I is described above.

Hancock *et al.*

Hancock *et al.* teaches an integrated microfluidic nucleic acid analysis system for MALDI-TOF mass spectrometry. The system is a small unit containing a variety of features such as apertures, microchannels and reaction zones for sample manipulation. The system also includes a MALDI ionization surface, which can be made from a variety of different materials. Hancock *et al.* teaches the purpose of the system is to handle and detect small amounts of sample with minimal sample loss.

Analysis

Claims 16-24 and 102 depend from claim 1. Claim 103 depends from claim 25. As discussed above, Zhang I does not teach or suggest numerous elements of claim 1 and claim 25, including delivering a defined and controlled volume such that spot-to-spot characteristics are reproducible in an array, and depositing material on a surface without touching the surface.

Hancock *et al.* does not teach or suggest that which is missing in Zhang I. Hancock *et al.* teaches a system with a variety of features including a MALDI ionization surface. Hancock *et al.* does not teach or suggest formation of an array of spots nor delivery without touching a surface. Hancock *et al.* does not teach or suggest delivering a defined and controlled volume such that spot-to-spot characteristics are reproducible. Therefore, the combination of Zhang I and Hancock *et al.* cannot result in the methods of claims 16-24, 102 or 103. Accordingly, the combination of teachings of the cited references cannot establish a *prima facie* obviousness rejection of claims 16-24, 102 or 103.

The Rejection of Claims 60, 86 and 104-107 as Obvious over Zhang I, Nelson *et al.* and Hancock *et al.*

Claims 60, 86 and 104-107 are rejected as obvious over Zhang I, Nelson *et al.* and Hancock *et al.* The Office Action asserts that the claims are obvious because Hancock *et al.* allegedly teaches materials recited in claims 60, 86 and 104-107, while Zhang I and Nelson *et al.* teach the underlying methods. This rejection is respectfully traversed.

Claims

Claim 60 is directed to the method of claim 40, where the substrate comprises material selected from the group consisting of silica, glass, cellulose, silicon, metal, plastic, polymer and metal-grafted polymer.

Claim 86 is directed to the method of claim 70, where the surface of the substrate is functionalized chemically, functionalized with beads or functionalized with dendrites of captured material.

Claims 104-107 are directed to the methods of claims 31, 40, 70 and 78, respectively, where the substrate comprises any one of or combinations of silicon, metal, plastic, a membrane, polymeric material, a metal-grafted polymer; and the substrate is optionally functionalized chemically, functionalized with beads, functionalized with dendrite trees of captured material and combinations thereof.

References

Zhang I, Nelson *et al.* and Hancock *et al.* are described above.

Analysis

Claims 60, 86 and 104-107 depend from claims 31, 40, 70 and 78. As discussed, Zhang I and Nelson *et al.*, singly or in any combination thereof, does not result in all

elements of claims 40, 70 and 78, including delivering a defined and controlled volume such that spot-to-spot characteristics are reproducible. Also discussed, the combination of teachings of Zhang I and Nelson *et al.* fail to teach or suggest the system of claim 31, and the Office Action presents no basis for rejecting claim 31. In particular, the cited references do not teach or suggest a movable arm, a controller for moving a movable arm, or a controller for controlling a vesicle to deliver a defined and controlled volume to the surface of a substrate, as recited in claim 31.

Hancock *et al.* does not teach or suggest that which is missing in Zhang I and Nelson *et al.* Hancock *et al.* teaches a system with a variety of features including a MALDI ionization surface. Hancock *et al.* does not teach or suggest formation of an array of spots. Hancock *et al.* does not teach or suggest delivering a defined and controlled volume such that spot-to-spot characteristics are reproducible. Hancock *et al.* does not teach or suggest a movable arm, a controller for moving a movable arm, or a controller for controlling a vesicle to deliver a defined and controlled volume to the surface of a substrate.

Since Hancock *et al.* is silent regarding delivering a defined and controlled volume such that spot-to-spot characteristics are reproducible, the combination of teachings of Hancock *et al.*, Zhang I and Nelson *et al.* also does not teach or suggest these elements. Furthermore, the combination of teachings of Hancock *et al.*, Zhang I and Nelson *et al.* does not teach or suggest a movable arm, a controller for moving a movable arm, or a controller for controlling a vesicle to deliver a defined and controlled volume to the surface of a substrate. Therefore, the combination of Zhang I, Nelson *et al.* and Hancock *et al.* does not teach or suggest all elements of claims 60, 86 and 104-107. Accordingly, the combination of teachings of the cited references does not establish a *prima facie* obviousness rejection of claims 60, 86 and 104-107.

Unexpected results demonstrate that the claimed methods and systems are unobvious

Pertinent to the rejections under 35 U.S.C. §103 is the showing of unexpected results. It is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole. *In re Sernaker*, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). Unexpected properties must always be considered when determining obviousness. A compound's structure and properties are

inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesh*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

As discussed in previous responses, the DECLARATION of record establishes results that are neither taught nor suggested by any reference of record. None of the cited references teaches or suggests that dispensing a plurality of defined and controlled volumes would result in an array of spots, where mass spectra of the material obtained from each spot are reproducible within the array of spots. As shown in the DECLARATION of record, mass spectra of the material obtained from each spot are reproducible within the array of spots. None of Zhang I, Nelson *et al.*, Zhang II, or Hancock, singly or in any combination thereof teaches or suggests the increase in reproducibility from spot-to-spot by delivery or deposition of defined and controlled volumes results in uniform spectra as shown in the DECLARATION of record. Therefore, as to the claims rejected under 35 U.S.C. §103, the Examiner has failed to set forth a *prima facie* case of obviousness.

In response to Applicant's demonstration of unexpected results, the Office Action states, "the examiner would rather expect non-obviousness of the results, if defined and controlled volumes of the sample material of the same content and concentration would not lead to reproducible results, especially taking into account indication of Zheng [*sic*] that small volume of the sample (~5 nL) is essential for sensitivity and reproducibility of MALDI MS spectra." As discussed herein, Zhang *et al.* does not teach or suggest that defined and controlled sample volumes are essential for sensitivity and reproducibility of MALDI MS spectra. The Office Action points to no other evidence of record to rely on the conclusion that the results described in the DECLARATION are expected results. Methods for achieving reproducible mass spectra are not a matter of common knowledge, and, therefore, the Office Action must point to some concrete evidence in the record in support of its holding that Applicant's results are not unexpected. *See* MPEP §2144.03, *In re Zurko*, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001). In the absence of such support, the Office Action cannot sustain its conclusion that results of the claimed methods would have been expected.

The Office Action impermissibly uses hindsight provided by Applicant's disclosure to assert that reproducibility of mass spectra from dispensing defined and controlled volumes would be expected. Zhang *et al.* teaches sensitivity and reproducibility resultant from

desalting and concentrating a sample, not from dispensing defined and controlled volumes (page 1771, left column, lines 11-16). Zhang *et al.* provides no expectation of reproducible mass spectra as a function of spot volume. Expectation of reproducibility of mass spectra from dispensing defined and controlled volumes can only be found in Applicant's disclosure, which is not allowed.

* * *

In view of the above remarks and the amendments and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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